CLEVENGER (S. V.)

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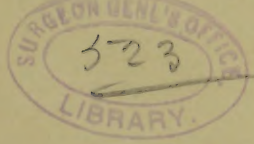

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By S. V. Clevenger, M. D., Chicago.

A theory of sleep phenomena, to be complete, must have data for its construction drawn from wider sources than we find have been surveyed in the average physiological essay on the subject.

Notwithstanding the strides made by biology, more particularly in its morphological aspects, the past quarter century has added but little to Wm. B. Carpenter's summary of "Sleep and Somnambulism," in his famous "Physiology," or what is contained in J. G. McKendrick's article in the Encyclopædia Brittanica. A full bibliography is given in the *Dictionnaire Encyclopédique des Sciences Médicales;* McNish, Durham, Kohlschütter, Pflüger and Mosso afforded the main discussions, which have been added to but little by later writers.

Herbert Spencer (Principles of Biology, Vol. I., Chap. IV.) on "Waste and Repair," summarizes much that could be more directly applied to a satisfactory consideration of the study than was required in his "Synthetic Philosophy."

Spencer notes that reptiles maintaining no great temperature and passing their lives mostly in a state of torpor, suffer but little diminution of mass by waste, but with the higher order of animals which are active and hot-blooded we see that waste is rapid, and when unchecked, bulk and weight decrease, ending very shortly in death. From these and allied considerations, he formulates the dictum that in the same creatures there is most waste when most motion is generated. Valentin computes the carbonic acid exhaled by the waking marmot as seventy-five times more than when it was hibernating, and the oxygen inhaled was forty-one times greater in the waking state. Invalids who are able to take scarcely any nutriment, by being kept warm and still, are able to lessen waste by thus reducing force expenditure.

Experimental comparison between the hibernating marmot and starving pigeon shows the latter loses forty times more muscular substance than the torpid marmot, eleven times more fat, thirty-three times more alimentary canal tissue, eighteen and three-tenth times more liver, fifteen times more lung, five times more skin, so that the parts least consumed in hibernation are the hydro-carbonaceous deposits which serve as a store of force, while in the awake and active pigeon, equally unsupplied with food, the greatest loss takes place in the motor organs. The diminished ability of bodily organs to perform their functions after activity, is noted. That legs, arms and eyes become enfeebled, and that concentrated attention prostrates the brain, are familiar truths.

Repair is everywhere and always making up for waste. While awake, waste is in excess and repair is going on, but not to the same extent as when asleep; though repair is at this time in excess, still some waste is necessitated by the carrying on of never-ceasing functions.

"During activity, the reintegration falls in arrears of the disintegration, until, as a consequence, there presently comes a general state of functional languor, ending at length in a quiescence which permits the reintegration to exceed the disintegration and restore the parts to their state of integrity."

Extending these considerations of Spencer and those who had previously written to the same effect, we are confronted with the fact that tissue restoration is undeniably a chemical process, and the queries arise, why, in such states as cerebral congestion, with its surplusage of blood, the brain may not rest, and why should sleep occur at all if there is proximity of food to the tissues undergoing waste?

Surveying the physiological accompaniments of sleep in all animal life, we find that in the simplest forms, surfeit and extreme privation arrest motions, and the rational explanation of this would be that the majority of molecules that compose such simple forms are relieved of tension, either by the completion of molecular construction or by their not having within combining reach, atoms with which combinations are possible.

Nutritive processes are certainly carried on during sleep, and the quiescence of sleep facilitates this action

by staying the waste of such tissues as are most in need of such reparation and, obviously, nourishment is transferred from such parts as can spare it best to those that are deficient in this regard. If repair were instant and incessant upon waste, then sleep would not be needed to transfer nutrition about the body, and one of the best evidences of this is that, often, massage may so redistribute blood and feed the jaded tissues as to largely take the place of sleep, at times rendering it unnecessary. At other times, massage or a warm bath may induce sleep more rapidly by starting a redistribution such as takes place normally during profound sleep.

If we look upon sleep as merely an *effect*, or an accompaniment, of a nutritive process, and as not in every case even a necessary one, we substitute a regard for the real instead of the apparent phenomenon.

In æstivation, amœbic encystment, hibernation, the absence of food requires quietude that will conserve what little there is present in the animal itself. In plethora, apnœa, etc., this quietude is enforced by the surcharged molecules being incapable of further assimilation, which drops the activity of the entire animal towards the lowest expression.

A parallel is afforded by the action of soil which at times agriculturists claim "needs a rest." It is conceivable that time may be necessary to effect certain chemical combinations even in the presence of the requisite elements for the soil restoration. Fertilizers of appropriate sorts may cover the exhausted soil, but time is needed for the assimilation of such fertilizers and the ground must lie fallow until its productive

capacity is regained, however long this may require; and very likely this necessity for a greater or less loss of time in building up complex cerebral or sarcodal structures explains why sleep occurs, and shuts off further decomposition until reconstruction can take place. The limit of comfortable activity having been reached, sleep takes place because further drain through waste may be distressing, and this discomfort becomes agonizing when prolonged, a fact taken advantage of by the Chinese as a method of torturing criminals.

Less heat and carbonic acid being produced during sleep further indicates the reduction in chemical decomposition that then occurs. Helmholtz estimates 40 calories produced during sleep and 112 when awake. "He who sleeps, dines," is an old saying, and much sleeps favors obesity.

Mass motion being suppressed in sleep enables molecular rebuilding the better, as the molecules are not then engaged in the major activities but eat, so to speak, themselves, while the body rests, just as workmen take an hour off to dine, and discontinue the work upon which they are aggregatedly engaged.

Whenever supply is constant to the animal or to its tissues, the necessity for sleep diminishes in proportion to the ability of such animal or tissues to rapidly reintegrate the compounds destroyed. The differences between the sleeping habits of animals are thus at once explained. It is conceivable that animals may exist whose nearly every cell is so constantly bathed in absorbable food as to place it comparatively beyond the need of sleep, but such animal, as a rule, could not

be very highly organized, or, like the sloth, could not be very active, and the rete mirabile in the axilla of the sloth shows how part of the muscular strain is provided for while the animal hangs to the tree.

A still further important factor in this connection I communiciated to *Science*, New York, Nov. 11. 1892, in an article entitled, "Preliminary Note on Sleep:"

That there is a relative anemia of the brain during sleep is well established, but the hypotheses advanced to account for this or any other of the sleep phenomena are unsatisfactory. In "Comparative Physiology and Psychology," 1884, I treated the subject briefly, and since then have been gradually accumulating and arranging data for a theory which I have finally adopted, and which appears to me to be fairly complete as enabling the major phenomena to be accounted for.

Briefly stated, where there is physiological waste there is, normally, repair, and the activities of the brain demonstrably are kept up by renewed nutrition derived from a blood supply adjusted to the ordinary needs. When there is cerebral anemia, as in chlorosis, then there is increased desire to sleep, the brain does not receive the necessary quantity to compensate waste, and it rests, just as any commercial activity will cease with withdrawal of means to continue it. Those who are familiar with my nutrient reflex theory, mentioned in the book referred to (Professor C. K. Mills of the Pennsylvania University, and Professor C. L. Herrick of the Dennison, Ohio, University, have

written approvingly thereon), will understand that with the cessation of sensory stimulation there will be less blood attracted to the brain and other nerve centers, the heart-beats lessen in vigor and number, and, with the pulse-rate fall, there is ordinarily less blood in the brain.

Now, it is evident that anemia of sleep is not caused by constricted blood vessels, else there would be the facial pallor seen during an attack of epilepsy, or paroxysm of anger or fright; and with this quieting of the brain processes by stimuli withdrawal, such as is afforded by darkness, silence and absence of irritation generally, a further lessening of molecular interchange in the brain occurs; and I claim that *it is the molecular activity in the brain that attracts the blood there chemically and mechanically,* and the sympathetic, or vaso-motor system has evolved to facilitate this regulation of demand and supply. Then, granting this, there will be during sleep a passive condition of the blood vessels, and the blood supply will fall to a minimum.

An extension of these considerations will enable all that pertains to sleep to be accounted for, such as aestivation, hibernation, insomnia, dreams, and all derangements of sleep.

At this stage we may conveniently condense what otherwise could easily fill a volume, in reviewing as much of sleep phenomena as may be necessary to test the consistency of this mainly chemical theory. Larval and fetal inactivity or sleep, the prolonged sleep of infants and the drowsiness of pregnant females

can be understood as demands for lessened activity during constructive processes. An army is recruited and accoutered before it fights, and the molecular cell building is the process of getting ready for the major life activities.

The suspension of consciousness during sleep is apparently due to the lessening of function of organs generally. Consciousness, being a function of the gray matter, or central nervous system, is in abeyance because the gray matter is undergoing reconstructive rest as well as other portions of the organism. Imperfect sleep and dreams are caused by this rest not being complete, the circulation in these centers being irregular.

Worry notoriously exhausts more than many kinds and degrees of work, and sleep overcomes the exhaustion produced by this as well as other excessive brain taxation. In such instances we have a painful cerebral activity, and the molecular breakdown is greater than in simple mental application.

Stimuli withdrawal ordinarily lessens the nutrient reflexes, less blood is forced to the head, and the fall of blood pressure in the medulla drops the heart beats to a lesser number through pneumogastric action. Closing the eye reduces optic excitation, noises are heard and the blood does not immediately fall to a minimum in the brain, hence sleep may not appear until time has passed. As the vaso-motor reflexes are less and less called upon, an ebb of blood finally admits of obtuseness to noises, etc., when they do occur. With the restoration of general cell nutri-

tion, the desire for activity increases and general reflexes are easier provoked. The nutrient reflexes of the brain now begin to send blood there upon stimulation, and the person awakes with the noises and light of day, or upon slighter provocation, if these are absent.

The instance is often cited of a boy who was blind and anesthetic, who fell asleep when his ears were closed to sounds.

But stimulation is a relative matter, for many who are accustomed to continuous noises become adjusted thereto, as does the miller who is awakened by the machinery stopping. In Arctic regions, also, the exclusion of light is not necessary to induce profound sleep.

Somnambulists have been separately classed as the speaking, the acting, the speaking and acting, and the hearing, seeing, speaking and acting. In all these, consciousness is absent, hence somnambulism is more or less automatism of important organs; dream acting. Sleep, to be complete, must overtake all portions of the body, and if from any cause irritation persists in any part, as during pain, then imperfect sleep results. It is conceivable that a speech center, centers for arm and leg movements, etc., may be hyperesthetic independently of the adjacent parts. Dr. George W. Jacoby, in a paper read before the New York Metropolitan Medical Society, Feb. 15, 1893, ably surveys the matter of "periodical sleep seizures of an epileptic nature," in which this sort of unconscious automatism is mentioned, and he believes that there is a relation-

ship between the corpulence in some of these cases, such as that of Dickens' fat boy, Joe, and perverted nutrition due to a pathological condition in the psychic centers. Dr. Jacoby concludes that "sleeping attacks, occurring alone or in combination with other symptoms, if of brief duration and followed by amnesia, are probably epileptic in character. If somnambulism, particularly of a noisy kind, is present, this probability becomes a certainty."

In narcolepsy, he claims that there is consciousness of what is going on during the attacks, the patient is not obtuse when awakened and he at once has full possession of his intellectual faculties. In this instance it would seem as though consciousness was the only faculty that was not asleep. Hysterical lethargy is associated with other evidences of the disease, such as more or less hemianesthesia. Hysterical sleep, in my opinion, is directly due to partial brain ischemia through contracted blood vessels to one or more parts. The amblyopia, deafness, aphonia, etc., could be also thus accounted for, as well as the fact that sudden impressions, or the cerebral suffusion produced by nitrite of amyl, cut short the attack.

The prolonged somnolence of cerebral syphilis, Buzzard (Diseases of the Nervous System, p. 288) assigns to the remarkably thickened walls of the arteries at the brain base—usually of a nodular character—diminishing the caliber of the vessels. Huebner, in Ziemssen's Cyclopædia, also has important observations upon this subject: "The consequence would appear to be that the cortical substance of the hem-

ispheres must be starved of blood to a considerable extent."

The great sleeplessness of mania for long periods and the supervening emaciation, show that not only cerebral but general rehabilitation is interfered with; waste is not only in excess of repair but the latter is seriously impeded by disease. Hence the necessity for sustaining treatment in this disorder. I have occasionally known stimulants to secure an abatement of the furor and produce sleep, when other routine measures merely added to the trouble. The hot bath, while temporarily beneficial, too often is followed by collapse, additionally going to show the necessity for sustentation in many of the cases that are frequently overdosed with depressants.

Warmth, judiciously used, however, is attended with good results. The fact that so many of the insane sleep best on hot nights should not be lost sight of. In Griesinger's "Mental Pathology and Therapeutics," page 75, et seq., sleep, in connection with insanity, is well considered, and he particularly compares insanity to dreaming.

Preyer originated the blunder that sleep was caused by a toxic substance in the blood, upon the inference that as fatigue was associated with sarcolactic acid in the muscles, the latter was the cause of the former. Pflüger regarded sleep as cerebral asphyxiation from excess of carbonic acid accumulation. On the other hand, recent experiments point to increased consumption of oxygen during sleep. Evidently, as a definite amount of nitrogenized hydro-carbonaceous matter is

consumed in all waking effort, cessation of activity lessens this consumption, but not to the extent of arresting it altogether, for the inevitable result would be a disintegration of the tissues.

The complex albumen molecule, C_{72} H_{112} N_{18} SO_{22}, with its 225 atoms, in undergoing metabolic changes, adds to and subtracts from its number of atoms within a certain range, and maintains its life and potencies. Let us say that twenty-five of its atoms are used up, exploded in exertion, and its limit of exhaustion has been reached. Plainly, these twenty-five atoms should be regained during comparative quiescence by other than toxic or asphyxiating means. In short, the cell eats while the colonial activity ceases, and this is the meaning, the end and aim of sleep. If, in addition, twenty-five more atoms enter into the combination, making it a still more complex molecule, a margin of fifty atoms may thus be imagined as enabling extra exertion within safe limits. Destructive metabolism could be supposed to ensue from several hundred of these atoms being parted with.

The chemical composition of the hypnotics affords no clue to their modus operandi. The mere presence of nitrogen in many is negatived by this element also occurring in ammonia and thousands of compounds with varying properties. Chlorine also appears as a food constituent in salt, as part of the anesthetic chloroform, and as a suffocant in its gaseous form. Neither the number nor the position of the atoms of carbon, hydrogen, nitrogen and oxygen in morphine explain why it differs from quinine which also contains these elements in other proportions.

Neither complexity nor simplicity of atomic combinations guarantees any explanation of the molecular rationale, but in a general way the more useful drugs have a constitution admitting of more or less direct conversion into animal constituents, and yet this is far from being a safe universal guide, for some of the deadliest poisons, even in small quantities resemble foods in their chemical structure.

In some instances, solubility modifies actions materially for better or worse, in others the looseness of the atomic make-up explains some effects, and the resistance to atomic splitting up, or the temperature necessary for decomposition, explains other effects. With what knowledge we possess we can formulate something in general from specific instances:

Alcohol, C_2H_6O, is rapidly assimilated and in a certain sense is a food. This rapid assimilation by reconstructing the tissue could account for its stimulant effect, and when there had previously been cell waste upon which the insomnia depended, the sleep-inducing properties of alcohol are accounted for. The stupidity that follows over-indulgence is precisely what would occur from cerebral tissue surfeit.

Morphine, $C_{17}H_{19}NO_3$, upon thorough consideration also falls into this dangerous food category. It, with alcohol, though less rapidly, enters into molecular combinations with nerve tissues and induces a certain exhilaration and subsequent dulling of the senses.

The exhilaration caused by oxygen and the stimulant effects and later anesthesia of nitrous oxide gas, without doubt are owing to the rapid assimilation of

these articles by the blood and nerve centers. The stimulant effects of all these agents could be ascribed to rapid atomic interchanges, such as occur with less swiftness and danger in the ordinary course of nutritive supply.

The warmer blooded birds take up oxygen more rapidly than mammals, and far more so than reptiles. The acidity of muscle and nerve substance in connection with blood alkalinity renders possible the conveyance of alkaloids, and makes it likely that soluble alkaloidal hydrocarbons of the neurotic group, assimilable by the organism, have sufficiently close molecular resemblances to the acid protagon as to account for their mutual affinities and bio-chemistry.

In the constitution of protoplasm, as well as that of any compound whatever, there is a necessity for the absence of certain molecular groupings which would destroy the combinations if integrity is to be preserved. The cell environment is reached by adaptability, and in the differentiation of cells it is easily seen that what would be nutrient to one may easily poison another by combustion conversion, as with sulphuric acid, or affinities in lesser degree existing between the toxicant and molecule.

The life of the cell depends upon the absence of these deleterious molecules for which there are affinities, precisely as animals must avoid fire. Prussic acid, HCN, presents the simplest example. The nitrogen therein is in a dangerously assimilable form, and its sudden surcharging of the nerve centers with carbonized blood paralyzes the body. Even though

the venous blood occurs after prussic acid has first caused the blood to appear to be arterialized, at least destructive chemical changes are instantly induced by this simply constructed poison. The action of nitroglycerin and of amyl nitrite exhibits the swiftness of union between the nitrogen and important structures. Nitrogen has a persistent tendency towards its free inert state, and this very disposition confers upon it great physiological importance. On the other hand, oxygen has a great antipathy to uncombined existence. These two mechanically mixed ingredients of the air play complementary parts in biological phenomena.

Certain drugs have special affinities for certain groups of nerves, and white pigs and sheep are said to be differently affected by vegetable poisons from colored individuals, a fact accounted for, doubtless, by the presence or absence of pigment compounds which have affinities for or resist the influence of certain poisons.

The antidotal action of chlorine gas in prussic acid poisoning may be due to the former directly lessening the surfeit (so to speak) imparted by the hydrocyanic acid. The sedative property of small doses of the latter show that it has a nutritive value which larger doses exaggerate poisonously.

The theory that chloral, C_2HCl_3O, liberates chloroform in the blood is tenable notwithstanding the definite urochloralic and other urinary excretion after chloral ingestion; but how does chloroform, $CHCl_3$, cause anesthesia? Its solvent power over sulphur, phos-

phorus and fatty bodies, conjoined with its primarily intoxicating properties, might make it appear to combine slight nutrient with destructive effects, the latter acting later but more powerfully.

The greater safety of ether with its stimulating property in small doses, point to the nutrient action outweighing its toxicity, or to the relative proportion of each being within safer amounts in ether.

It is doubtful if the bromides become substitution compounds in any of the animal tissues, further than to pervade the secretions and lessen activity by taking the place of nutrient materials. About as free nitrogen dilutes the air and lessens the quantity of oxygen respired, so may the inert bromide salts saturate the circulation in place of other materials that could enter into combination. If bromide salt ingestion passes a certain point, distressing insomnia may result, probably from the anemia exceeding what ordinarily occurs in sleep. Chloral, also, in large doses may utterly fail to do anything but cause distressing wakefulness and gastric irritability, especially in senile debility associated with heart disease. The significance of this being, that waste is but increased by the chloral. Alcoholics in such instances act promptly and beneficially for easily understood reasons.

Ergot has an indirect hypnotic effect through its contraction of the blood-vessels, upon the muscles of which it acts directly. Winckler's discovery of a coloring matter in secale, closely resembling hematin, might mean that oxygenation of the involuntary muscles is accomplished by ergot, and the contractility is thereby induced.

Though, strictly speaking, phenacetine and phenocoll can not be classed as hypnotics, their effects as sedatives and certain chemical considerations make them specially interesting as neurotics.

The antipyretic effects of acetanilid and phenacetin when combined with acids are destroyed; the earliest discovery of the kind being that of Ehrlich, that the acid sulphone group abolished the affinities of certain substances which they previously possessed for the nervous system. The existence of so many alkaloids having this affinity, taken in that connection, afford hints that some of the combining efficacy of neurotics depend upon the union of a base and radical in the nerve tissues, notwithstanding the fact that these alkaloids may be introduced into the system combined with sulphuric or other acids; such acidulation being looser than in the coal-tar series.

An ingenious introduction of the basic glycocoll into the group whence phenacetin is derived, rendered it much more soluble, and to this extent increased its ease of administration without altering the antipyretic and analgesic properties of phenacetin when thus converted into phenocoll.

Glycocoll (also known as glycocin, and amido-acetic acid) is the base which, united with the phenetidine group, forms phenocoll and renders it soluble. This base being an amido-acid, on the principle enunciated above, phenocoll should be a safer and more effective antipyretic and sedative than phenacetin.

Unlike the majority of synthetical antipyretics, phenocoll, according to Kobert of Dorpat, is not pois-

onous to animals and does not affect the blood. It has a slight stimulant effect upon the circulatory system. Phenacetin is closely allied chemically to acetanilid, and physiologically both phenacetin and phenocoll act as a modified acetanilid or antipyrin. What particular change in the construction accounts for this modification, only great advances in biochemic knowledge will reveal; but it can be conjectured that differences in the closeness with which nitrogen as well as other atoms are held in a compound, may unlock a molecule quicker or retard its entering into new combinations.

Considering the derivation of paraldehyde, its somnifacient influence might be regarded as similar to that caused by alcohol. The ordinary ethyl or acetic aldehyde being alcohol minus two atoms of hydrogen, and paraldehyde is formed by the condensation of three molecules of aldehyde into one molecule. It is so easily split up, so sensitive to oxidizing agents, and so much care is required in securing a pure article, that with safer and better hypnotics in the field paraldehyde is not likely to come into general favor. Not only has the pungent aldehyde been found in it as an admixture but the poisonous amyldehyde also.

Urethane and its derivative, somnal, have been pretty well abandoned by physicians.

Were it not for chloralamid, which is rapidly superseding all modern synthetically constructed hypnotics, sulphonal would have remained in high esteem. In treating the insane, sulphonal has the advantage of solubility in hot tea or coffee, and can therefore be

given without the patient's knowledge. The common practice of administering the dry sulphonal leads to undesired effects, such as a prolonged but unsatisfactory drowsiness or stupidity usually the day after it is taken, The action of sulphonal has apparent reference to its alcoholic derivation through mercaptan. The derivatives, trional and tetronal, possess few if any advantages over the original drug, while it is claimed that the latter sometimes caused vomiting.

The substitution of chloral for opium created an epoch in therapeutics, nothwithstanding the fact that chloral was found to have very disagreeable after-effects and some dangers in its use. The advent of sulphonal enabled chloral to be largely superseded, but finally the discovery of chloralamid affords us all the advantages of chloral in the absence of its disadvantages.

The poisonous dose of chloral hydrate is not established; small doses have caused death, and large doses have been tolerated. Idiosyncrasies caused wide variance in effects.

Chloralamid requires slightly larger doses than chloral, but the former causes what resembles ordinary physiological sleep to a far greater degree than is induced by chloral. In other respects the drugs are closely allied, except that the deleterious properties of chloral appear to be absent from the newer compound. Particularly the gastric irritation induced by chloral frequently destroys its usefulness, and chloralamid has no such influence upon the stomach, nor is it an irritant to any mucous membrane.

Some laboratory experiments of Kny of Strassburg, demonstrated that chloralamid was free from action upon the heart and disgestive tract, nor did it cause congestion and the other unpleasant after-effects of chloral, though he inferred that the latter was slowly released in the circulation from chloralamid, and its depressant effects were counteracted by the formamide, which acted as a stimulant.

Thirty years ago, formiate of ammonium was used by Ramskill in the London Hospital for the Epileptic and Paralytic. He considered it useful in chronic paralytic diseases with general torpor, and he thought that it had a special tendency to the nervous centers Formic acid is a circulatory stimulant, but too energetic to be useful except when chemically combined. It is one of the fatty acid series and has been found to exist in small quantities in the spleen, pancreas, thymus, muscle and brain, and in leucocythemia in the blood, urine, sweat and marrow.

An important group of animal constituents, called the amido acids, is derived from the fatty acids by replacing one or more hydrogen atoms by the radical amidogen NH_2. This includes leucin, tyrosin, glycocin, taurin, creatin.

As the amines, amides and amido-acids are nitrogenous organic compounds among the simpler organic proximate principles, it is a safe assertion to make that the union of the formamid with the chloral in chloralamid justifies the classing of this new preparation *among the nutrient hypnotics*; that is, among those like alcohol, which, when properly administered, supplies

material that has been exhausted in the nervous centers, notwithstanding the superficial objection that some of these organic compounds are decomposition products.

Reasonably, much of the toxic influence of chloroform may be ascribed to the solvent power of that anesthetic over sulphur, phosphorus and fatty bodies, as these substances are important ingredients of nerve tissue. Now if this toxic effect is obtunded or prevented by the union of chloral with formamid through the former expending this deleterious solvent propensity upon the latter, and the formamid being so closely allied to the normal nitrogenous proximate principles as to act practically like a food, which we can all the readier assume from its slight stimulant effect upon the circulation, the combined nutrient and toxic effect of chloral in that drug and chloroform is replaced by *an almost wholly nutrient hypnotic in the compounding of chloralamid.*

The published attestations of physicians as to the usefulness of chloralamid are so numerous, but at the same time so uniform, that brief mention of most of the references would swell this article unduly.

There has been a notable absence of any disposition to decry the drug in any quarter worth attention. In the use of every hypnotic, as well as any other therapeutic agent, bungling administration occurs, but this should not discredit rational exhibition. We may as well inveigh against water because it drowns.

Briscoe, of Chicago, accounts for a few failures through some practitioners using hot liquids as a vehicle, when chloralamid should never be offered in any other than cold solution.

In my experience, the elixir has a delayed action as compared to the powder dissolved just before use, an effect for which I have not tried to account.

The fact that chloralamid is about one-half as expensive as sulphonal, and moreover superior to it, one would imagine would be inducement for hospitals to purchase it in preference to the older and costlier hypnotic; but in certain quarters the error prevails that chloralamid is only soluble in alcohol. This arises from the fact that in twenty parts of water chloralamid dissolves very slowly at ordinary temperatures, between 60 and 70° F. Where, for any reason, it is not desirable or convenient to use the small amount of alcohol, about a minim and a half to the grain, in preparing it for use, the aqueous solution can be prepared beforehand, half a day, or kept in the dispensary stock in that form.

Brandy or raspberry syrup are the most used vehicles; a drop or two of dilute hydrochloric acid to the ordinary dose facilitating solution.

It is to be hoped that the mistake so often made in giving sulphonal dry, will not be made in chloralamid administration, as its action may be delayed until the next day and cause a stupid half wakefulness not at all desirable.

Dr. Joseph Collins contributed to the *Journal of Nervous and Mental Diseases* (July, 1892), an excellent review of his experience with chloralamid in insomnia associated with various troubles, such as phthisis, pneumonia, neurasthenia, alcoholic delirium, senility, chorea, sciatica, lithemic headache, overwork, opium habituation, meningitis, and reports that he was particularly

struck with its efficacy in two conditions, viz.: pain and excessive irritable activity of the brain.

An important feature he notes, in the treatment of certain cases, is to beware of giving drugs which will in any way militate against the excretion of deleterious matters from the system and lower the condition of vascularity, such as the preparations of opium and the bromides.

"In conditions where chloral is indicated," states Dr. Collins, "but some intervening symptoms contra-indicate its use, such as weak heart and respiration, as in the asthenic stage of acute disease, or in diseases of the heart and lungs, chloralamid can be substituted with safety and with good results."

He sums up in favor of its safety and reliability, its absence of after effects, such as headaches, and its value as a hypnotic where pain or cerebral activity are prominent factors.

Taking other authors at random, we find that as to the time of action, personal idiosyncrasy determines differences, but to no greater degree than was observed with chloral, the average limit being from one-half to three hours intervening between the dose and its effect, the duration of sleep varying from two to nine hours.

In many forms of mental disease, chloralamid acted beneficially in relieving insomnia; regular sleep was induced in chronic alcoholics and in patients suffering from locomotor ataxia, even when they had been taking large doses of morphine. Other ailments in which sleeplessness occurred were alleviated to the extent of sleep procuring by chloralamid, as follows: Cardiac asthma,

chorea, neuralgia, rectal carcinoma, hysteria, spinal disease, delirium of cerebral hemorrhage, rheumatic fever, thoracic aneurism, gastric carcinoma, hepatic carcinoma, bronchitis, cephalalgia, chlorosis with mitral insufficiency, endocarditis and renal colic.

It has been effectively used as a sedative in seasickness, neuralgias and the sufferings of gastric ulcer.

The United States Dispensatory designated chloral as the most efficient soporific and the one most often used, and claimed that for producing sleep no medicine equaled it except opium, and to this it was preferable as wanting the properties which render opium inapplicable in certain cases, as in active congestion and acute inflammation of the brain and to a certain degree in constipation of the bowels.

In the rapidly accumulating literature of the subject, we begin to note that where chloralamid appeared to be ineffective in a certain disorder, in the experience of one author, other physicians obtained good results from its administration in the same ailment. In short, the history of chloral discussion is repeating itself in some of the contradictory experiences, but with the advantage for the later drug, that, wherever chloral has been established as of use, chloralamid proves not only more satisfactory, but where through deleterious properties contraindications for chloral using forbid its use in a large list of diseases, chloralamid has been proven to be perfectly safe. No hypnotic has won so universal favor in as short a period and without the arraignment against it of occasional unfortunate episodes.

The largest dose on record used at one time is

reported by Dr. Lackersteen, *Medical News*, November 25th, 1893. A patient swallowed a mixture containing 140 grains of chloralamid with about 40 grains of bromides and fully recovered from the stupor which followed.

Personally I have found it useful in facial neuralgia in small doses, and often sleep was induced by from fifteen to thirty grains when pain had previously prevented rest, showing that chloralamid has sedative or analgesic effects.

The restlessness of anemic states has been allayed by small doses, and in a few cases I have substituted chloralamid for the bromides in treating epilepsy with apparent benefit, alternating the drugs or using them conjointly so as to diminish the dose of each. It would require at least a year's experimentation in this disease with chloralamid to enable a more conclusive statement than that it has been satisfactory as far as used by me; but I have not excluded other medicines at these times except for such short periods in treating epileptics that not only will a lengthened period be required to determine how far chloralamid is useful in this ailment, but I would prefer to hear from numerous other physicians who may make similar trials, before pronouncing unqualifiedly in favor of its continued use in epilepsy.

Against the distressing activity of hemichorea in adults, which destroys rest and prevents sleep for so long as to imperil life, I hope much from chloralamid as I had previously found that chloral was absolutely the only remedy that would afford the required sleep for a few hours at a time; had chloralamid been then

known it could have been continuously used where the chloral had to be withdrawn owing to the stomach irritability it induced, substituting a source of danger equally grave. Dr. Barrs, of Leeds, reports good effects from chloralamid in ordinary chorea. Some reports from psychiatrical institutes venture statements to the effect that chloralamid is good in one psychosis and not in another. Now the trials have been far too few to enable such assertions to be extended generally.

There is a strong probability that a large percentage of all cases of insomnia in the insane can be relieved by judicious chloralamid exhibition, particularly if attention is paid to accompanying conditions and general physiological treatment is adopted at the same time. To merely impute the sleeplessness to brain disorder and give a hypnotic without reference to the condition of the heart, liver, kidneys, or emunctories generally, would be extremely irrational, and would fully account for failures in some instances. At times I have found that the insane patient would be affected differently by the same dose from no discoverable cause, but where proper attention has been paid to the general bodily condition, as a rule, good results were secured with chloralamid.

In delirium tremens, it is only common sense to see that elimination is carried on properly, and often eliminants alone will end the furor of alcoholism.

In some of the congestive attacks of paretic dementia, ergot, if anything, would prove more useful, but paretics will secure sleep from chloralamid ordinarily, as well as other patients.

I have found it useful in the sleeplessness and painful cerebral states of melancholia, and particularly so in the case of one recurrent melancholiac whose relapses were cut short by the prompt action of the drug.

In cerebral and spinal syphilis, pain is assuaged markedly by chloralamid, but of course it should not be given where there is a stuporous tendency, nor with expectation of anything but amelioration.

In the traumatic neuroses it is particularly valuable. Several cases of Erichsen's disease from concussion of the spine were enabled to secure sleep from chloralamid when ergot, massage and hot water applications which had previously been helpful had failed.

If the small doses of chloralamid, when substituted for bromide of potassium, are found to be generally applicable, I do not believe that ill effects can follow from the abuse of the chloralamid in this way, at all comparable to what has been experienced in the wretched overdosing of the bromides. At least the anemia and mental hebetude produced by bromides will be escaped from by the substitution. And how far these small doses of chloralamid can be properly used remains to be ascertained, but my experience has been satisfactory enough to lead me to continue their use in many of the nervous affections where irritabitity or pain are prominent.

There is such a thing as the chloral habit which is much more rapidly stopped than the opium addiction, but whether it is too early to assert that there is or is not a chloralamid habit, certainly nothing denoting any

liability to habituation has been prominently mentioned, though so far as that is concerned any drug that proves serviceable in continued suffering may be used too long, and the only question of concern is what undesirable consequences may come from such prolonged use. If chloralamid is a reconstituent hypnotic there can be no such bad effects following its over-indulgence as are recorded against opium and chloral.

It would be folly to expect that any single remedy for insomnia would be available in all instances, for just as sleepless states may be caused by any of the multitude of maladies to which the body is liable, so must there be numerous appropriate measures of relief, when relief is at all possible. The advice, to seek and remove the cause of sleeplessness is sensible enough, though in too many instances the cause is only conjectural. Nevertheless, a rational system of hypnotic use can be secured on a physiological basis, and with far more satisfactory results if we duly regard the cause of the loss of sleep and existing bodily conditions. For example, a dose of ergot in some hyperemic states may relieve pain or cause sleep by lessening the vascular tension upon which these disabilities depended. A hot bath may distribute the circulation and act derivatively upon organs which, when congested, caused the distress and wakefulness. Massage acts similarly when scientifically applied, and when unskilfully made use of may add to the discomfort; for example, if derivation from the head is set up by massage it will relieve cerebral hyperemia, but add to cerebral anemia, so this method must be resorted to

with full knowledge of the physiological results aimed at.

In a general way, we may classify hypnotic action as accomplished by derivation, such as by removing irritative quantitative causes; by elimination of quantitative or qualitative causes, as of some toxic agent; reconstructive action by resupplying parts in states of defective nutrition; sometimes by minimizing activity until rehabilitation can overtake waste with supply; by restoring normal function as with digitalis or alcoholics. The least desirable of all methods being such as merely stupefy and overload the circulation with effete or poisonous material through interfering with elimination, or by destructive changes induced in nerve tissues or the blood upon which the nerves depend for sustenance.

So eliminative functions should be kept in good repair, if possible, when almost any kind of a hypnotic is given, particularly such as are likely to add some toxic material to the system; but the ideal sleep procurer would be one that abstracted nothing from the nervous system that it contained normally, nor added thereto anything deleterious; and as sleep is a process of repair or feeding of the nerves and their ganglionic centers, still more effective would be whatever caused sleep by repair of such waste; and unless credible evidence to the contrary appears in the course of time, we are in possession of such a hypnotic in chloralamid.

70 State St., Chicago.

CHLORALAMID IN NERVOUS AND MENTAL AILMENTS.

By S. V. Clevenger, M.D., Chicago.

The administration of chloralamid is too often made unnecessarily complicated, and when the very simple method I have adopted comes into general use, I am sure that this most superior hypnotic will supplant very largely the array of harmful sleep-inducing potions, particularly in hospitals and asylums.

I usually put sixty grains of the chloralamid crystals in a half pint bottle, three-fourths filled with ordinary drinking water, neither warm nor cold, but just as it issues from the hydrant; a vigorous shaking for a few seconds starts the solution; setting aside for three or four hours, without corking, so as to admit air, then a few additional shakes, at irregular intervals, suffices to dissolve all or nearly all of the chloralamid. Or larger quantities can be prepared in hospitals in the morning in about the proportion of two or three ounces of water to the dose of fifteen grains, and by night it is ready for use. The slightly bitter taste is rarely objectionable, but any suitable addition can be made, such as raspberry syrup, whiskey, brandy, or a few drops of hydrochloric acid to assist solution and to modify the taste.

In large asylums or hospitals the aqueous solution is the easiest made and most effective; doing away with the alcohol which is not indispensable, and which by many is supposed to counteract the effect of the drug.

A fifteen grain dose may be thus given hourly or half hourly, up to sixty grains if necessary, without fear of disagreeable consequences.

One physician afflicted with the cocaine habit, who was under my care, exceeded instructions and took ninety grains nightly, from which he procured a restful sleep and was helped thereby to break off his terrible addiction, which had made him a fiend indeed. Another patient who had broken off whiskey excesses took ninety grains nightly, and experienced no ill effects beyond a sensation of tipsyness the next morning. The drunkard said the chloralamid took the place of his dram so effectually as to make him feel exhilarated, and as he sincerely wished to get over his failings, he voluntarily gave up his chloralamid also, for fear that he might rely upon it too much; but the ease with which he, and others, have relinquished this hypnotic indicate that *there is no chloralamid habit* in the sense of the word "habit" as connected with so many other drugs.

About the only objective results I have noticed from a nightly dose of ninety grains is an inclination to stagger a little the next morning, and so far from this being due to any depressant or toxic influence patients spoke of feeling a little exhilaration, such as wine affords. Even with such large doses there were no headaches or upset stomachs, and in such particulars the vast dissimilarity between chloral hydrate and chloralamid is seen.

For six months I have had under my constant care a young man afflicted with nocturnal epilepsy of the perambulating kind, a true somnambulism of the see-

ing, hearing, speaking, and acting variety. Soon after coming to my sanitarium at Riverside, Illinois, he arose one night and attempted to leave the house in his night clothes. He fought the nitrite of amyl inhalation so successfully that attempts to give it were a failure, and several strong attendants had all they could do to keep him in the room and themselves from harm. He bit, scratched, yelled and destroyed clothing with a mad man's ferocity, and bent back the thumbs of his guards in an attempt to break them off. This was previous to his taking any medicine. During the day he was a model of gentlemanly behavior, and assisted in his treatment rationally and anxiously.

I began with sixty grains of chloralamid nightly, dissolved in water, conjoined with treatment for his lighter attacks of *haut mal* during the day, and four months passed with but a mere suggestion of his former trouble, which had been of weekly occurence. At this writing he continues the nightly dose of chloralamid without the least derangement of health being apparent therefrom. On the contrary his memory is vastly improved, his capacity for sustained effort of all kinds is better, and during the past two months neither the nocturnal nor diurnal attacks have appeared. Two spells of *petit mal* occuring, if they can be called such, when there was no loss of consciousness.

Although his medicines included KI, AmBr, antipyrin, acetanilid, phenocoll (it is just as well to drop the hydrochloride or hydrochlorate appendix, which serves to confuse the druggist and physician, just as we usually omit hydrate from chloral hydrate), digitalis, cathartics, and occasionally sulfonal, *my main reliance was upon the chloralamid* for its evident ability to allay brain irritability in his case.

The chloralamid effectually quelled a dull headache from which he formerly suffered more particularly at night; and with this superb opportunity to test the drug

I can not only endorse Dr. Dana's report (*N. Y. Medical Record*, June, 1893) that chloralamid is a useful adjuvant in epilepsy, but can go further and say it is in many respects, for nocturnal epilepsy especially, better than most antiepileptics.

I would recommend the substitution of from fifteen to thirty grains of chloralamid nightly in lieu of a retiring dose of any bromide in mixed epilepsy, where attacks occur at night as well as in the day; and for severe nocturnal attacks from thirty to sixty grains.

To sum up the advantages of this treatment from the experience gained by six months' continuous administration of sixty grains nightly in this case:

Chloralamid suppressed nocturnal epilepsy and somnambulism completely.

It relieved the dull headaches originating in a meningo encephalitis, chronic from infancy, with epilepsy.

It afforded a refreshing sleep, from which the patient could be aroused as from natural sleep.

There was no derangement whatever of visceral functions.

The appetite was good, and intelligence and energy increased.

The sleeplessness and irritability due to head injuries are invariably lessened greatly by chloralamid, and in the instance of a furnace feeder, who, with delusions of persecution, had distressing hallucinations of hearing of an accusatory character, it was very interesting to observe his insanity gradually fade away, through the recuperating sleep chloralamid gave him, and finally to note his recognition of the subjective nature of his "voices" as they lessened and finally vanished.

In acute mania large doses of chloralamid, aided somewhat—but at times a "knock out,"—by such as sulfonal, was demanded in the patient's behalf. Formerly I used conium maculatum, but recently, where

chloralamid proves too mild, resort to sulfonal for its stupefying effects as a depresso-motor,—it is safer than conium, but as undesirable in the long run. Where continuous hypnosis is desired, I think *there is nothing on earth like chloralamid* in a large percentage of cases that are not helped by hygienic or other simpler means.

Conjoined with attempts to keep up elimination in melancholia with disturbed rest, chloralamid is better than sulfonal or any other hypnotic. In one sleepless case of agitated melancholia who refused food and had to be fed artificially, I mixed the chloralamid solution with the milk that was fed to her through the nasal tube, with the result of keeping her asleep during the night. Some authors mention that sulfonal thus given is followed by an inclination to take food voluntarily. This was my experience with chloralamid, with the advantage that the subsequent stupidity and increase of bowel turpidity attendant upon sulfonal administration in such cases were absent. The rest the patient obtains aids recuperation, and it is the latter and not the medicine (except indirectly) that inclines the patient to eat. When sleep is afforded to such cases the tendency to recovery is increased, other things being equal.

Dr. Emanuel Friend, of Chicago, reports a case of suffering from gonorrheal rheumatism wherein a grain of morphia nightly had been used for a month. Chloralamid was substituted in fifteen to sixty grain doses, and, to the surprise of the doctor and patient, sleep was secured each entire night, the daily pains were markedly diminished, and the craving for morphine, which was previously imperative, completely ceased. "Why couldn't I have had the drug before?", he asked a couple of days after beginning its use. In two weeks, through this and other treatment, he recovered enough to be about and sleep without the chloralamid dose.

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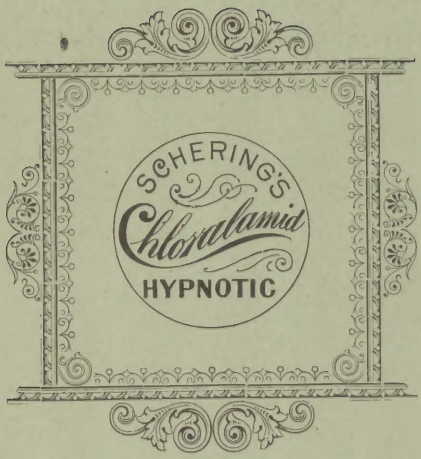
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